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REMARKS

Claims 44-67 and 92-115 are pending in the application. Claims 49-55, 61-67, 97-103, and 109-115 have been allowed. Claims 44-48, 56-60, 92-96, and 104-106 have been rejected. No claim has been amended. A claim listing is provided for the Examiner's convenience.

Voicemail

Applicant notes that claims 107 and 108 were neither allowed nor rejected in the Office Action and that two Gu (1997) references were cited, whereas only one Gu (1997) reference is of record. On June 10, 2008, Applicant's representative phoned the Examiner and left a message requesting clarification on these two issues. The Examiner responded with a voicemail on the same day to the effect that claims 107 and 108 were rejected, as were other claims directed to a medium, and that the second Gu (1997) reference should have been Gu (1998). Applicant's representative thanks the Examiner for his quick response.

Claim Rejections – 35 USC § 103

Claims 68-91, 92-96, and 104-106 were rejected as obvious over Franze et al. (US Patent No. 6,673, 575, *hereinafter*, Franze). Since claims 68-91 are no longer pending, the rejection of these claims is moot. The Office Action states that Franze suggests the use of fructose, galactose, and mannose and the use of combinations of sugars in culture medium for cells producing recombinant, sialylated proteins. Franze also recites CHO cells. The Office Action states, "It would have been obvious to use the sugars in different combinations because Franze suggests that combinations are beneficial and because it is a well established proposition of patent law that no patentable invention resides in combining old ingredients of known desired function where the results obtained thereby are not more than the additive effect of the ingredients. . . . The depth of the prior art is significant and clearly it has established that the selection of sugar, amounts thereof and other normal culture parameters are result effective variables. . . . "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover

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the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)." Office Action, page 4.

Applicant relies on arguments made in detail in papers dated October 11, 2005, April 10, 2006, December 20, 2006, October 29, 2007, and November 28, 2007 and respectfully requests that these arguments be reconsidered. In addition, new arguments are put forward below.

Applicant asserts that Franze is inoperable as a reference because the teachings in Franze mentioned above (*i.e.*, that addition of mannose, fructose, and galactose to medium singly or in combination can increase glycosylation) are experimentally unsupported in Franze and are contradicted by other teachings in the art and in the instant specification. A reference used in an obviousness rejection is presumed operable, but applicants may rebut operability by showing inoperability by a preponderance of the evidence. MPEP § 716.07 and 2121. This means that an applicant must show that it is more likely than not that the teachings of a reference are inoperable. If applicant meets this burden, the burden shifts to the PTO to show that the reference is, in fact, operable. *In re Sasse*, 629 F.2d 675, 681 (Cust. & Pat.App. 1980). As explained in more detail below, Applicant submits that the burden of showing inoperability of Franze by a preponderance of evidence has been met and respectfully requests either rebuttal of this showing or allowance of the rejected claims.

As discussed in previous responses Franze discloses the use of fructose, mannose, and galactose, as well as a huge genus of other carbohydrates and combinations thereof. (Applicants have argued extensively in previous papers filed October 11, 2005, April 10, 2006, December 20, 2006, October 29, 2007, and November 28, 2007 that a patentable species of the genus disclosed in Franze is being claimed.) The only combination of sugars for which any experimental results, well-controlled or otherwise, is reported in Franze is the combination of galactose, mannose, and glucose. Undisputed statements in the Declaration of Carole Heath, filed December 20, 2006 (*hereinafter*, the Heath Declaration) assert that one of skill in the art would not expect to be able to use all monosaccharides and disaccharides, or even the eleven sugars named in Franze, interchangeably in a cell culture process. Heath Declaration, page 4. *Therefore, the results disclosed in Franze would not be generalized by one of skill in the art to mean*

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that all carbohydrates or combinations thereof would behave in the same way as the combination of mannose, galactose, and glucose.

Moreover, the experiments of Examples 5 and 7, as reported in Franze, would not lead one of skill in the art to any unambiguous conclusions regarding even the one combination of carbohydrates tested. Given the undisputedly high level of skill in the art and the experimental controls described in Franze, one of skill in the art would be unable to unambiguously conclude what experimental factor was responsible for the observed results in Examples 5 and 7 of Franze. Heath Declaration, pages 1-4. Thus, statements in Franze indicating that the addition of carbohydrates can cause the changes in glycosylation are not supported by *any* experimental evidence that would lead one of skill in the art to believe that this is indeed the case. Applicant therefore asserts that Franze is inoperative as a reference for the teachings referred to in the Office Action.

In addition, published experimental evidence has shown that a number of relevant embodiments encompassed by the generic disclosure of Franze do not function as predicted in Franze. *See e.g.* Stark and Heath (1979), Archives of Biochem. Biophys. 192(2): 599-609; Nyberg, Ph.D. Thesis, MIT, 1998; Baker et al. (2001), Biotechnol. Bioeng. 73: 188-202. Applicant submits that these publications predate the publication of Franze in 2004, and it is therefore highly unlikely that any of them could have had any interest in invalidating Franze when they were published. The Patent Office has a duty to look at the art as a whole when evaluating obviousness, not merely to select individual references or portions of individual references. *In re Hedges*, 783 F.2d 1038, 1041 (C.A.Fed. 1986); *Panduit v. Dennison*, 810 F.2d 1561, 1566 (C.A.Fed. 1987). Therefore, these references should be considered along with Franze from the point of view of one of skill in the art. In particular, Nyberg shows that addition of a combination of galactose and mannose or addition of a number of different individual sugars, including mannose, fructose, and galactose, to CHO medium does not affect N-glycan site occupancy of a protein produced by the cells. Stark and Heath showed that addition of glucose or mannose stimulated protein glycosylation, whereas addition of fructose, galactose, and a number of other sugars did not. Baker et al. found that addition of glucosamine and uridine to NSO and CHO cells led to slight decreases in protein sialylation in both cell lines. Addition of ManNAc had no effect on protein sialylation of

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either CHO or NSO cells. These experimental data directly contradict unsupported teachings in Franze to the effect that addition of mannose, fructose, galactose, or any other carbohydrate to medium of CHO cells, either singly or in any imaginable combination, will increase protein glycosylation. Therefore, Applicant submits that this published evidence, *which is supported by controlled experimental data*, is more than adequate to show that the relevant teachings of Franze are more likely than not in error.

Further evidence of the inoperability of Franze comes from experimental evidence of record in the instant case and in foreign oppositions, as well as data reported in the instant application. Kadoya et al., submitted in an Information Disclosure Statement dated December 20, 2006; Specification, Example 1, Figure 2. Looking back through the long file history in the instant case, Applicant can find no mention of Kadoya et al. in any Office Action and respectfully requests that this reference be considered if it has not been already. Kadoya et al. show that the results disclosed in Franze were not achieved when CHO cells, rather than the human cells used in Franze, were used. As noted in the response dated October 29, 2007, the assignee of Franze has now taken a position in Europe that reflects a view that the data in Kadoya et al. show that the invention described in Franze is not operable in CHO cells. This certainly constitutes a preponderance of evidence that the invention of Franze is not operable in CHO cells. In addition, Figure 2 in the instant application shows that only specific combinations of sugars, not all combinations, were effective to increase protein sialylation, thus provided additional data showing that some relevant embodiments encompassed by the generic disclosure of Franze are not operable. Therefore, Applicant submits that sufficient evidence to show that the relevant disclosure of Franze is more likely than not in error has been provided, and respectfully requests that the PTO rebut this showing if Franze is relied upon in future rejections.

Applicant further submits that a proper *prima facie* case of obviousness has not been stated because it rests on *In re Aller*, which is factually distinguishable from the present case and is therefore not applicable. In *Aller*, the claims were directed to a process for decomposing isopropyl benzene hydroperoxide comprising the steps of bringing the peroxides into contact with aqueous sulphuric acid at a concentration between 25 and 70% at a temperature between 40 degrees and 80 degrees, thereby

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producing phenol and acetone. The prior art reference taught a similar process performed at a temperature of 100 degrees C and with a 10% sulphuric acid solution. The court found that, in general, differences in temperature or in concentration of a chemical reagent in a previously known process would be unlikely to merit patentability absent a new and unexpected result that differs in kind from previous results. *Aller*, 220 F.2d 454, 456. The results of using the claimed process, although somewhat superior to those reported in the prior art reference, were not found by the court to be so vastly different as to merit patentability. *Aller*, 220 F.2d 454, 457.

The addition of different sugars to medium (as in claims 44, 56, 92 and 104) to influence protein sialylation is dissimilar from adjusting the temperature of a chemical reaction or the concentration of one of the reactants because it was *not* commonly known in the art at the priority date that the addition of these sugars could increase protein sialylation. References of record show, *as a matter of experimental fact*, that different sugars have different effects on protein glycosylation and that not all sugars, including some of those recited in the claims, cause increases in glycosylation. *See e.g.* Stark and Heath (1979), Archives of Biochem. Biophys. 192(2): 599-609; Nyberg, Ph.D. Thesis, MIT, 1998; Baker et al. (2001), Biotechnol. Bioeng. 73: 188-202. Undisputed factual evidence of record states that one of skill in the art would not expect all monosaccharides and disaccharides to have similar effects on protein glycosylation. Heath Declaration, pages 4-5. Franze, on the other hand, makes experimentally unsupported statements and claims that addition of any carbohydrate or any combination of carbohydrates to a medium can increase protein glycosylation in any kind of mammalian or insect cells. Franze, col. 2, line 64 to col. 3., line 3, col. 3, lines 21-30, and claims 1 and 4. Given the high level of skill in the art, it is simply not reasonable to suppose that one of skill in the art would believe each and every statement in Franze, in spite of the fact that many statements in Franze are directly contradicted by published experimental evidence. Thus, the characterization of the selection of sugars and amounts thereof as "result effective variables" is misplaced when the prior art is viewed as a whole. Quite simply, the claimed combinations of sugars, unlike the reaction temperature and reactant concentration of *Aller*, were *not* known to have effects protein sialylation, either singly or in combination, prior to the filing of the instant application. The generic disclosure of

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Franze, which asserts that all carbohydrates would increase glycosylation would not be taken seriously by one of skill in the art (*see* Heath Declaration) in view of experimental evidence to the contrary.

More on point than *Aller* is *Application of Antonie*, 559 F.2d 618 (Cust. & Pat.App. 1977). In *Antonie*, the invention was a wastewater treatment device comprising a tank and a continuously rotating "contactor," which aerated both microorganisms growing on the contactors and the wastewater itself. In particular, the claimed device had a ratio of tank volume to contactor area of 0.12 gal/sq.ft. A prior art reference described a structurally similar device and disclosed that the degree of purification of the treated water ("efficiency") could be increased by increasing the contactor area. The application on appeal asserted that the claimed ratio gave a "maximum treatment capacity," where a given contactor area was providing maximum "efficiency" (i.e. degree of purity) for a given "throughput" (gal/day) or maximal "throughput" for a given "efficiency." The prior art reference did not discuss this issue of essentially getting the most out of a given piece of equipment, and the experiments suggested in the reference would not have revealed the property that the applicants had discovered. The court therefore concluded that *Aller* was not applicable in this case because the parameter optimized by the applicant was not recognized to be a result effect variable in the prior art reference. This is also the case in the instant application where mannose, fructose, and galactose were not known in the art to increase protein sialylation in CHO cells either singly or in combination before the priority date of the instant application. Thus, as in *Antonie*, these sugars are not "result effective variables," and the claimed invention is therefore nonobvious.

Claims 44-48 and 56-60 are rejected as obvious over Franze in view of Schnaar et al. (US Patent No. 6,274,568, *hereinafter*, Schnaar), and Wood (US Patent No. 6,472,175, *hereinafter*, Wood) or Gu et al. (1997) or Gu et al. (1998). As explained in detail above, Applicant submits that Franze is an inoperable reference, that the logic of *Aller* is not applicable to the instant case, and that these rejections are therefore overcome. In addition, Applicant relies on the numerous arguments submitted in previous papers and requests that they be reconsidered.

To summarize current and past arguments, Applicant submits that all claims are nonobvious for the following reasons. First, Franze is an inoperable reference for all the

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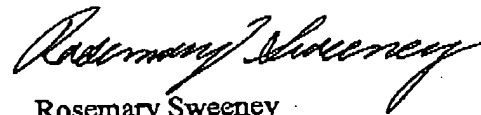
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reasons explained above, and all claims are therefore allowable. Applicant submits that this has been shown by a preponderance of evidence and that the burden now rests on the PTO to rebut this showing if Franze is to be relied upon in future rejections. Second, the rejected claims are nonobvious species over the huge genus of different media containing carbohydrates and combinations thereof described in Franze. Moreover, no reason has been articulated why one of skill in the art would have selected the claimed media containing combinations of particular carbohydrates. Third, there is a lack of reasonable expectation of success as explained in previous papers. Fourth, the results described in the instant application were not predictable and were unexpected. Fifth, the sugars added to the claimed media gave more than additive effects. In other words, each element of the claims did not perform the same function it did separately. Sixth, not all claim elements are disclosed in an operable reference. Seventh, the art has not been considered as a whole. Finally, the assignee of Franze has tacitly admitted (by claim amendments made in a European opposition) that the invention described in Franze is not operable in CHO cells. For all these reasons, Applicant submits that all claims are nonobvious and requests notice to that effect.

CONCLUSION

Applicant respectfully requests allowance of the claims. Should the Examiner believe that any outstanding issues can be best addressed via teleconference, he is invited to contact the undersigned at the direct dial number listed below.

Respectfully submitted,



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